

Current Trends of “Nanotechnology” in Pharmaceutical

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ABSTRACT

Size reduction is one of most fundamental unit operation which is of prime importance in pharmacy. It helps in improving stability and bioavailability, reducing toxicity, enhancing release and providing better formulation opportunities for drug.

In the recent trends, the drugs in nanometer size range have found to increase the performance in variety of dosage forms. The word ‘nano’ is a Latin word, which means ‘dwarf’. Nano size refers to 10^{-9} of a particular unit thus nanometer is 10^{-9} of a meter.

Nanotechnology is the science that deals with the processes that occurs at molecular level and of nanolength scale size. Nanotechnology has shown tremendous progress in many fields but in pharmaceutical fields are yet to be explored, although, it has powerful impact in various medical fields such as biophysics, molecular biology, bioengineering, cardiology, oncology, ophthalmology, endocrinology immunology etc. Nanotechnology provides intelligent system, devices and materials for better pharmaceutical applications.

The current status of nanotechnology in pharmaceutical field includes development of Nano medicine, tissue engineering, nano robots, biosensors, biomarkers etc. Pharmaceutical Nanotechnology provides opportunities to improve materials, medical devices and help to develop new technology where existing and more conventional technologies may be reaching their limits. Thus in the coming years advancements in this field will led to the improved form of drug delivery as well as other prospects of medicine and pharmacy.

KEYWORDS: Pharmaceutical Nanotechnology, Nano scale, Drug delivery, Bio nanotechnology

INTRODUCTION

Size reduction is one of the fundamental unit operation having important applications in pharmacy. It helps in improving solubility and bioavailability, reducing toxicity, enhancing release and providing better formulation opportunities for drugs. Drugs in the nanometer size range enhance performance in a variety of dosage forms. Major advantages of nano sizing include:

1. Increased Surface Area,
2. Enhanced Solubility,
3. Increased Rate of Dissolution,
4. Increased Oral Bioavailability,
5. More Rapid Onset of Therapeutic Action,
6. Less Amount of Dose Required,
7. Decreased Fed/Fasted Variability,
8. Decreased Patient-To-Patient Variability.

Nanotechnology and nano science are widely seen as having a great potential to bring benefits to many areas of research and applications. The term “nanotechnology” was first used in 1974, when Norio Taniguchi, a scientist at the University of Tokyo, Japan, referred to materials in nano meters .

Nanotechnology is a multidisciplinary field which literally means any technology on a nanoscale that has applications in the real world. Nanotechnology is the science that deals with the processes that occur at molecular level and of nano length scale size (i.e. 10^{-9}) .

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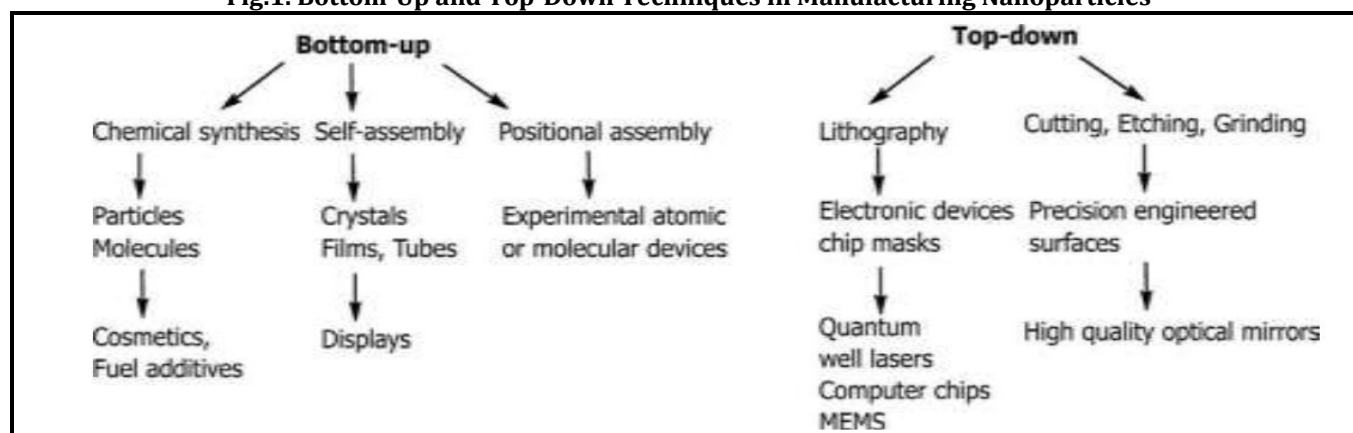


The properties of materials at the nano scale can be very different from those at a larger scale. When the dimension of a material is reduced from a large size, the properties remain the same at first, and then small changes occur, until finally when the size drops below 100 nm, dramatic changes in properties can occur. If only one length of a three-dimensional nanostructure is of nano dimension, the structure is referred to as a **quantum well**; if two sides are of nanometer length, the structure is referred to as a **quantum wire**. A **quantum dot** has all three dimensions in the nano range. Materials can be nano structured for new properties and novel performance. **Nano particulate drug delivery system** may offer plenty of advantages over conventional dosage forms, which includes improved efficacy, reduced toxicity, enhanced bio distribution and improved patient compliance. Pharmaceutical nano particles are subnanosize structure, which contain drug or bioactive substances with in them and are constituted of several tens or hundreds of atoms or molecules with a variety of sizes (size from 5 nm to 300 nm) and morphologies (amorphous, crystalline, spherical, needles, etc). Nano scale materials and devices can be fabricated using either “bottom-up” or “top-down” fabrication approaches. In bottom-up methods, nano materials or structures are fabricated from build up of atoms or molecules in a controlled manner that is regulated by thermodynamic means such as self-assembly. Alternatively,

advances in micro technologies can be used to fabricate nano scale structures and devices. These techniques are collectively referred to as top down nanofabrication

technologies, include photolithography, nano molding, dip-pen lithography and nano fluidics (Figure 1)

Fig.1. Bottom-Up and Top-Down Techniques in Manufacturing Nanoparticles



NANODEFINITIONS

'**Nanoscience**' can be defined as study of phenomenon and manipulation of materials at atomic and molecular scales.

'**Nanotechnology**' is related to design characterization, production and applications of structures, devices and systems by controlling shape and size at nanometer scale.

'**Nanomedicine**' is defined as submicron size ($<1\mu\text{m}$) modules, used for treatment, diagnosis, monitoring, and control of biological system.

'**Pharmaceutical nanotechnology**' embraces applications of nano science to pharmacy as nano materials, and as devices like drug delivery, diagnostic, imaging and biosensor.

'**Nanometrology**' is the science of measurements at the nano scale. Four commonly used techniques are: transmission electron microscopy (TEM), scanning electron microscopy (SEM), and scanning probe techniques [scanning probe microscopy (SPM)], and optical tweezers (single-beam gradient trap).

'**Nanotoxicology**' refers to the study of the interactions of nanostructures with biological systems with an emphasis on the relationship between the physical and chemical properties of nanostructures with induction of toxic biological response.

'**Bionanotechnology**' generally refers to the study of how the goals of nanotechnology can be guided by studying how biological "machines" work and adapting these biological motifs into improving existing nanotechnologies or creating new ones.

'**Nanobiomechanics**' (also bio nanomechanics) is an emerging field in nano science and biomechanics that combines the powerful tools of nano mechanics to explore fundamental science of biomaterials and biomechanics. For example, it has been shown that red blood cells infected by malaria are 10 times stiffer than normal cells

SCOPE AND OPPORTUNITY

Applications of nanotechnology to pharmacy, that provide intelligent and smart drug delivery systems, is expected to emerge as most important and powerful tool as an alternative to conventional dosage form.

Pharmaceutical nanotechnology is most innovative and highly specialized field, which will revolutionize the

pharmaceutical industry in near future. Pharmaceutical nanotechnology presents revolutionary opportunities to fight against many diseases. It helps in detecting the antigen associated with diseases such as cancer, diabetes mellitus, neurodegenerative diseases, as well as detecting the microorganisms and viruses associated with infections. It is expected that in next 10 yrs. market will be flooded with nanotechnology-devised medicine.

The scope of pharmaceutical nanotechnology is very wide from smart material for tissue engineering to intelligent tools for delivery of drugs and diagnostics, and more recently, artificial RBC etc. Current applications of nanotechnology in pharmacy are development of nano medicine, tissue engineering, nano robots, advance diagnostic, as carrier of diagnostic and therapeutic modalities and as biosensor, biomarker, image enhancement device, implant technology, bioactive surfaces etc. A large number of nano systems, which have been investigated in pharmacy to date, are liposomes, dendrimers, metallic nano particles, polymeric nano particles, carbon nano tubes, quantum dots, nano fibres etc.

PHARMACEUTICAL NANOTECHNOLOGY BASED SYSTEMS

Pharmaceutical nanotechnology provides two basic types of nano tools viz. nano materials and nano devices, which play a key role in region of pharmaceutical nanotechnology and related fields.

Nano materials are biomaterials used, for example, in orthopedic or dental implants or as scaffolds for tissue-engineered products. Their surface modifications or coatings might greatly enhance the biocompatibility by favoring the interaction of living cells with the biomaterial. These materials can be sub classified into nanocrystalline and nano structured materials

Nanocrystalline materials are readily manufactured and can substitute the less performing bulk materials. Raw nanomaterials can be used in drug encapsulation, bone replacements, prostheses, and implants.

Nanostructured materials are processed forms of raw nanomaterials that provide special shapes or functionality, for example quantum dots, dendrimers, fullerenes and carbon nanotubes. Nanodevices are miniature devices in the nanoscale and some of which include nano- and micro-electromechanical systems (NEMS/ MEMS), microfluidics

(control and manipulation of micro or nanolitre of fluids), and microarrays (different kind of biological assay e.g. DNA, protein, cell, and antibody). Examples include biosensors and detectors to detect trace quantities of bacteria, airborne pathogens, biological hazards, and disease signatures and some intelligent machines like respirocites.

NANOPARTICULATE DRUG-DELIVERY SYSTEMS

An ideal drug-delivery system owns two elements:

- A. The ability to target
- B. To control the drug release.

Targeting ensures high efficiency of the drug, reduction in the side effects, especially when dealing with drugs that are presumed to kill cancer cells but can also kill healthy cells when delivered to them. The reduction or prevention of side effects can also be achieved by controlled release of the medicament to the target. Nano particulate provides a better penetration of the particles to the body as their size allows delivery through intravenous injection or other routes.

Lipid-Based Colloidal Nano drug-Delivery Systems

Lipid nano capsules are submicron particles which are made up of an oily liquid core surrounded by a solid or semisolid shell. Colloidal drug carriers have a number of potential advantages as drug delivery systems. Some advantages are better bioavailability for poorly soluble drugs, use of physiological lipids, the shunning of organic solvents in the preparation process, a wide potential application spectrum including oral, dermal, and intravenous.

The common disadvantages include: particle growth, unpredictable gelating tendency, unexpected dynamics of polymorphic transitions, and inherently low incorporation capabilities because of crystalline structure of the solid-liquid nanoparticles

Recent Trends in Solid-Lipid Nanoparticle Research

Recently, a lipid-based solvent-free formulation process has been developed to prepare lipid nanocapsules in the nanometer range. This process takes advantage of the variation of the hydrophilic-lipophilic balance of an ethoxylated hydrophilic surfactant as a function of the temperature, leading to an inversion phase.

Polymeric Micelles as Drug Carriers Systems

Polymeric micelles have attained attention in drug delivery, partly due to their ability to solubilize hydrophobic molecules, their small particle size, good thermodynamic solution stability, extended release of various drugs, and prevention of rapid clearance by the reticuloendothelial system (RES). Critical micelle concentration (CMC), similar to low-molecular-weight surfactants, is the key characterization parameter for polymeric micelles. Furthermore, various types of drugs can be loaded into the hydrophobic core of polymeric micelles by chemical conjugation or physical entrapment of polymeric micelles by utilizing various interactions such as hydrophobic interactions, or ionic interactions, or hydrogen bonding. The hydrophobic core serves as a reservoir from which the drug is released slowly over a longer period of time.

POLYMER-BASED NANOPARTICULATE DRUG DELIVERY SYSTEMS

1. Hydrogel-Based Nanoparticulate Drug-Delivery Systems.
2. Dendrimer-Based Drug-Delivery Systems.
3. Calcium Carbonate Nanoparticles.

4. Protamine-Based Nanoparticulate Drug Carriers (Proticles): Protamine is a nonantigenic and virtually nontoxic peptide from the sperm, the compound derived from salmon, the most widely used source, and has a molecular mass around 5000 g/mol. It can be used as a carrier system for delivery of DNA or oligonucleotides and it is being used as the cationic component.

5. Chitosan-Based Nanoparticulate Drug-Delivery System: Chitosan, a polycationic polymer, consisting of d-glucosamine and N-acetyldglucosamine linked by β -(1, 4)-glycosidic bonds, has been widely used for NPDDSs for delivering anticancer drugs, genes, and vaccines. Chitosan is a natural polymer and biocompatible. Chitosan nanoparticles also have been evaluated for ocular applications.

6. Silicone Nanopore-Membrane-Based Drug-Delivery System.

7. Albumin and Gelatin Nanospheres.

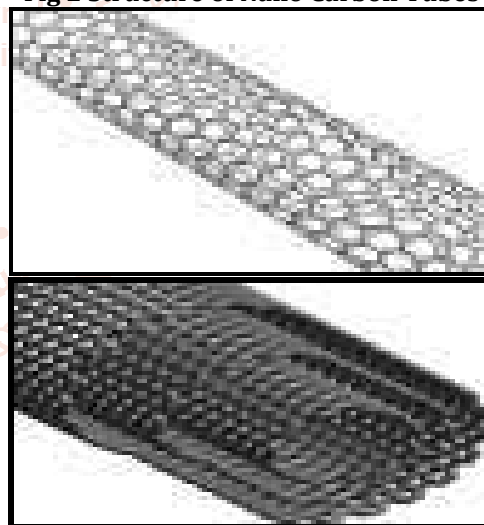
8. Polymeric Nanocapsules as Drug Carriers.

9. Polystyrene Nanospheres.

TYPES OF PHARMACEUTICAL NANOTOOLS

1. **Carbon Nanotubes:** These are hexagonal networks of carbon atoms, 1 nm in diameter and 1–100 nm in length, as a layer of graphite rolled up into a cylinder. There are two types of nanotubes: single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs), which differ in the arrangement of their graphene cylinders.

Fig 2 Structure of Nano Carbon Tubes



(a) Single walled (SWNTs) (b) Multi walled (MWNTs)

2. **Quantum Dots:** Quantum dots (QDs) are semiconducting materials that have a semiconductor core (CdSe), coated with a shell (e.g., ZnS) to improve its optical properties, and a cap that helps improving solubility in aqueous buffers. Quantum-dots have a large impact on some important development in different medical areas like diagnostic tools (magnetic resonance imaging, MRI), in vitro and in vivo detection and analysis of biomolecules etc.

3. **Dendrimers:** These are highly branched, treelike structures and have different compartments of chemical polymer. Dendrimer contains three different regions: core, branches, and surface. They have promising properties for delivery of bioactives ranging from drugs, vaccines, metal, and genes to desired sites. Their hollow interior provides space to incorporate drugs and other bioactive physically or by various interactions to act as drug delivery vehicles. Most

important applications of dendrimers are solubilization, gene therapy, dendrimer based drug delivery, immunoassay and MRI contrast agent. (Figure 3).

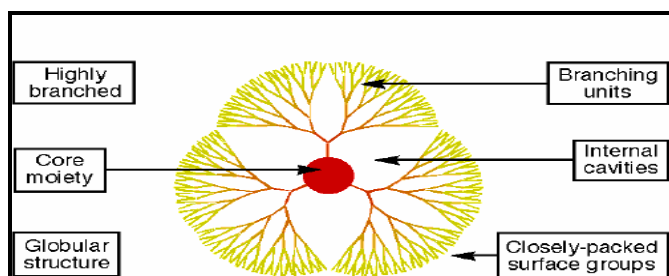


Fig 3 Schematic Representation of Dendrimer

4. Liposomes: These are closed vesicles that are formed when dry phospholipids are hydrated. Liposomes are classified into three basic types based on their size and number of bilayers. Multilamellar vesicles (MLVs) consist of several lipid bilayers separated from one another by aqueous spaces. Small unilamellar vesicles (SUVs) and Large unilamellar vesicles (LUVs) consist of a single bilayer surrounding the entrapped aqueous space. (Figure 4).

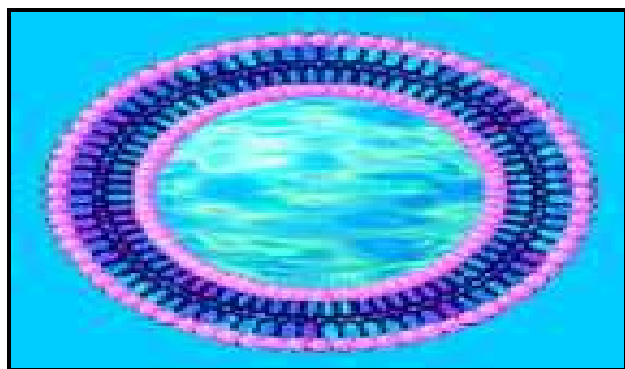


Fig 4 Structure of Liposomes

5. Polymeric Micelles: Polymeric micelles are usually of <100 nm and are amphiphilic block copolymer having supramolecular core-shell structure.

6. Polyplexes/ Lipopolyplexes: These are assemblies, which form spontaneously between nucleic acids and polycations or cationic liposomes (or polycations conjugated to targeting ligands or hydrophilic polymers), and are used in transfection protocols.

ENGINEERING OF PHARMACEUTICAL NANOSYSTEMS

Since nanosystems are the chemical entity, they are not easily accepted for bio-delivery of the drug. They need some modifications to make them compatible for biological delivery, by altering their size and surface by biocompatible polymers and with some site specific ligands. Some modifications are

1. Functional Nanosystem: The modification in the properties of nanosystems by the incorporation, adsorption or covalent coupling of components like polymers and/or ligands to their surface is known as surface functionalization. Some commonly employed tools for surface modification are polymers, carbohydrates, endogenous substances/ligands, peptide, protein, nucleic acid and polysaccharides. These tools make the nanosystems an intelligent tool and that offers large varieties of properties like higher biostability, lower aggregation and high target specificity in comparison to conventional nanosystems.

2. Multifunctional Nanosystems: Multifunctional nanosystems can be developed in three ways firstly

multifunctionality imparted to the core for the simultaneous delivery of two or more therapeutic active moieties; secondly as multifunctionality imparted to surface for stabilization by PEG (poly ethylene glycol) for the modification in circulation time, and use of targeting moiety and thirdly as multifunctionality imparted to material by using thermal sensitive, pH and stimuli sensitive biomaterials.

NANOTECHNOLOGY IN DRUG DELIVERY: NANOPARTICLES

The ultimate goal of application of nano-drug delivery systems is to develop clinically useful formulations for treating diseases in patients. Clinically useful drug delivery systems need to deliver a certain amount of a drug that can be therapeutically effective, and often over an extended period of time. Such requirements can be met by the micro scale drug delivery systems manufactured by nanotechnology. In addition, little attention has been paid to the fact that the systems have to be introduced into the human body, requiring approval from the Food and Drug Administration (FDA). The current methods of preparing nano/micro particles are mainly based on double emulsion methods or solvent exchange technique 14-15. Nano-design of drugs by various techniques like milling, high pressure homogenization, controlled precipitation etc., are explored to produce, drug nano crystals, nano particles, nano precipitates, nano suspensions (which for ease of understanding commonly mentioned as nano crystals). Controlled drug-delivery strategies have made a dramatic impact in medicine. In general, controlled-release polymer systems deliver drugs in the optimum dosage for long periods, thus increasing the efficacy of the drug, maximizing patient compliance and enhancing the ability to use highly toxic, poorly soluble or relatively unstable drugs. Nano scale materials can be used as drug delivery vehicles to develop highly selective and effective therapeutic and diagnostic modalities.

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10 -1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nano particles, nano spheres or nano capsules can be obtained. The major goals in designing nano particles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen

PREPARATION OF NANOPARTICLES

A. Dispersion of preformed polymers by:

1. Solvent evaporation method.
2. Spontaneous emulsification/solvent diffusion method.
3. Salting-out/ emulsification diffusion method.
4. Production of nanoparticles using supercritical technology.
5. Polymerization methods.
6. NPs prepared from hydrophilic polymers.

B. Polymerization of monomers:

Nanoparticles have been prepared most frequently by three methods:

1. Dispersion of preformed polymers;
2. Polymerization of monomers;
3. Ionic gelation or coacervation of hydrophilic polymers.

APPLICATIONS OF PHARMACEUTICAL NANOTOOLS

Size reduction is helpful in overcoming various physiological, biochemical and pharmaceutical barriers. Pharmaceutical nanotechnology provides wide array of systems or device of nanosize, which offer numerous benefits. Some important applications areas are:

1. As nanomaterials for tissue engineering:

Nanotechnology offered numerous smart materials that are used for tissue repair and replacement, implant coatings, tissue regeneration scaffolds, structural implant materials, bone repair etc.

2. Nanobased drug delivery tools: These are polymeric nanoparticles, liposome, dendrimer, polymeric micelles, polymer-drug conjugates, antibody- drug conjugates, which can broadly be classify as:

- A. Sustained and controlled delivery system,
- B. Stimuli sensitive delivery system,
- C. Functional system for delivery of bioactives,
- D. Multifunctional system for combined delivery of therapeutics, biosensing and diagnostic.
- E. Site specific targeting (intracellular, cellular, tissue).

Furthermore, nanobased drug delivery tools are now being employed in the treatment of various diseases such as in cancer therapy etc.

a) **Cancer treatment:** Nanotechnology can have a revolutionary impact on cancer diagnosis and therapy.

b) **Implantable delivery systems:** Nanotechnology is opening up new opportunities in implantable delivery systems because of its size, controlled and approximately zero order release which otherwise may cause toxicity when compared to intravenous administration (due to first order drug kinetics).

c) **Site specific drug delivery:** Several approaches are now being tested for better site-specific delivery using liposomes, polymeric micelles, dendrimers, iron oxide, proteins using manipulation in passive and active uptake of drug.

d) **Gene therapy:** In gene therapy, a normal gene is inserted in place of an abnormal disease-causing gene using a carrier molecule. Conventional uses of viral vectors are associated with adverse immunologic, inflammatory reactions and diseases in the host. Nanotechnology enabled delivery systems have currently emerged as potential vector and are shown to be effective and promising tool in systemic gene treatment.

3. Molecular Diagnostics: Molecular imaging is the nanoscience of representing, characterizing, and quantifying subcellular biological processes in intact organisms. These processes include gene expression, protein-protein interaction, signal transduction, cellular metabolism, and both intracellular and intercellular trafficking. They have been successfully utilized in various magnetic resonance imaging, optical imaging, ultrasonic

imaging and nuclear imaging. (Table 3)

4. Biosensor and Biolabels: A number of analytical tools have been developed with application of this smart and potential technology. These tools are used for determination of various pathological proteins and physiological-biochemical indicator associated with disease or disrupted metabolic conditions of body.

A **biosensor** is generally defined as a measurement system that consists of a probe with a sensitive biological recognition element, or bioreceptor, a physicochemical detector component, and a transducer in between to amplify and transduce these signals in to measurable form.

5. Drug discovery: Pharmaceutical nanotechnology is playing crucial role in drug discovery that rely on better understanding of mechanism of the drug action and identification of biomarker associated with specific disease. Nanotechnology helps identification and validation of target by identifying the protein present on the cell surface or target surface. Nanotechnology will enhance the drug discovery process, through miniaturization, automation, speed and reliability of assays.

COMMERCIALLY AVAILABLE NANOPARTICLES

A. Melamine Nanospheres: Plain Polymethyl Methacrylate and Biodegradable Polylactide Nanospheres.

B. Magnetic Plain Dextran Nanospheres.

C. Gold Nanospheres: Gold particles are high quality nanospheres that can be used in the production of diagnostic tests as well as conjugation studies of proteins and antibodies. The particles have a very narrow size distribution and are available from 2 to 250 nm.

D. Silver Nanospheres: Silver nanospheres are high quality nanospheres that can be used in the production of diagnostic tests as well as conjugation studies of proteins and antibodies. The particles have a very narrow size distribution and are available from 2 to 250 nm.

E. Silica Nanospheres: This mono-disperse silica particles having a density of 2.0g/cm³ are easier to dispense and to separate. The silica particles are stable in water and organic solvents, produced under a new drying method. Silica particles are easy to functionalize and available as fluorescent particles. They are useful for coupling of DNA, oligonucleotides, oligopeptides, proteins, lectins, and antibodies.

Targeted Nano-Pharmaceuticals 'Targeted nano-pharmaceuticals' are designed to better target drugs towards diseased cells, tissues and organs. Diseased cells tend to have specific features on their surface named biomarkers. The targeted nano-pharmaceuticals contain drugs and selectively recognize and bind to the biomarkers on the cells. The drugs are then released locally, resulting in more effective targeting of the diseased cells. Precise targeting of the drugs can reduce side-effects in other parts of the body. Better targeting also allows higher doses to be administered locally while minimizing the side effects for the patient. Chemotherapy treatment for cancer for example is known to have severe side effects, and the aim is to reduce such negative consequences for the patient by using more precisely targeted nano-pharmaceuticals.

Discovering the right biomarkers to target for a certain disease is a key challenge for medical research. Nano pharmaceuticals may include contrast agents that allow the physician to see the location of the disease (e.g. tumour) on the image of a body scan, for instance with Magnetic Resonance Imaging (MRI), X-Ray Computed Tomography (CT) or Positron Emission Tomography (PET). The images can thereby show the location and extension of the disease

and can also be used for 'therapy monitoring', i.e. monitoring the effectiveness of the therapy over time

CHALLENGES TO PHARMACEUTICAL NANOTECHNOLOGY

Pharmaceutical nanotechnology has provided refined diagnosis and focused treatment of disease. However some ethical, scientific, social and regulatory issues posing various challenges in practical realization of pharmaceutical nanotechnology. Some major health risk associated with such devices includes cytotoxicity, translocation to undesired cells, acute and chronic toxicity; some unknown, unpredictable and undefined safety issues, environmental impacts of nanomaterials and non-biocompatibility. There are no specific FDA directives to regulate pharmaceutical nanotechnology based products and related issues. Although some FDA approved nanotechnology based products, which have entered the market are liposome, nanoparticles, monoclonal antibody based product, polymer drug conjugate, polymer-protein conjugate and some polymeric drugs. All-together these challenges caused urgent need to regulate these nanotechnology based products and delivery devices.

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